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Summary

Background Patients with relapsed or refractory acute myeloid leukaemia have a poor prognosis. Outcomes with conventional intensive salvage chemotherapy are suboptimal. We aimed to evaluate the safety and activity of high-dose cytarabine and mitoxantrone in combination with venetoclax in patients with relapsed or refractory acute myeloid leukaemia.

Methods This study was a multicentre, open-label, single-arm, phase 1/2 trial. Patients aged 18–75 years, medically fit for intensive chemotherapy (ie, Eastern Cooperative Oncology Group performance status ≤2, adequate hepatic and renal function) with relapsed (haematological relapse from first or second complete remission) or refractory acute myeloid leukaemia (no response after one or two courses of standard induction chemotherapy) were eligible. Patients received venetoclax 400 mg orally once a day on days 1–14 (initial 3-day dose ramp-up), mitoxantrone 10 mg/m² intravenously once a day on days 5–7, and cytarabine (dose level 1, 200 mg/m² continuous intravenous infusion on days 4–10; dose level 2, cytarabine 500 mg/m² intravenously twice a day on days 3–5; or dose level 3, cytarabine 1000 mg/m² intravenously twice a day on days 3–5). Phase 1 applied a 3+3 dose-escalation design to determine the primary endpoint of maximum tolerated dose and recommended phase 2 dose. The primary endpoint of phase 2 was the composite complete remission rate by intention-to-treat. Safety was assessed in all patients exposed to venetoclax. The trial is registered with EUDRA-CT, 2018–003025–28, and ClinicalTrials.gov, NCT04330820, and is completed.

Findings From April 6, 2020, to Aug 31, 2023, 55 patients were enrolled (12 in phase 1 and 43 in phase 2). Median follow-up was 30·8 months (IQR, 26·6–34·1). Median age was 57 years (IQR, 49·0–66·5). 30 (55%) of 55 patients were male and 25 (45%) were female. 25 (45%) of 55 patients had adverse-risk acute myeloid leukaemia according to the European LeukemiaNet 2022 classification and 19 (35%) had previous allogeneic haematopoietic cell transplantation (HCT). The maximum tolerated dose was not reached, and dose level 3 was considered safe and defined as the recommended phase 2 dose. The composite complete remission rate was 75% (95% CI 61–85, 41 of 55 patients). The most common all-grade adverse events were febrile neutropenia (29 [53%] of 55 patients), pneumonia (12 [22%]), and sepsis (12 [22%]). 15 serious adverse events occurred in 14 (13%) patients, of which sepsis and pneumonia were the most common. Potential treatment-related deaths were reported in four patients (sepsis n=3, pneumonia n=1).

Interpretation High-dose cytarabine and mitoxantrone plus venetoclax appeared to be safe, showed promising activity, and could be a new therapeutical approach for medically fit patients with relapsed or refractory acute myeloid leukaemia, especially as a bridge to allogeneic HCT.

Funding AbbVie.

Introduction

Patients with relapsed or refractory acute myeloid leukaemia have an unfavourable prognosis. Conventional salvage chemotherapy is associated with poor outcomes. Weighted mean complete remission rates in commonly used intensive, cytarabine-based regimens such as high-dose cytarabine and mitoxantrone (HAM), mitoxantrone, etoposide, and cytarabine, or fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin (FLAG-IDA) are 50%, 52·5%, and 52·9%, respectively.[1–4] Accordingly, median overall survival is short, ranging between 2·1 months and 11·0 months.[1] Thus, relapsed or refractory acute myeloid leukaemia remains a major clinical challenge.

Venetoclax in combination with hypomethylating agents or low-dose cytarabine has shown high

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Research in context

Evidence before this study

The outcome of patients with relapsed or refractory acute myeloid leukaemia is poor. Complete remission rates achieved with conventional intensive salvage chemotherapies alone, such as high-dose cytarabine and mitoxantrone (HAM) or fludarabine, cytarabine, granulocyte-colony stimulating factor, and idarubicin (FLAG-IDA) are low (40–50%), and corresponding overall survival is generally short. It was unclear whether combining intensive salvage chemotherapy (ie, HAM) with venetoclax would improve outcomes. Between Dec 16, 2017, and Oct 15, 2025, we searched PubMed using search terms "acute myeloid leukaemia", "AML", "relapse", "refractory disease", "mitoxantrone", "HAM", and/or "venetoclax". At the time the RELAX study was designed, no clinical data were available on venetoclax in combination with intensive chemotherapy, let alone in combination with HAM. Since the study's design, two larger prospective clinical trials reporting outcomes of patients with relapsed or refractory acute myeloid leukaemia treated with intensive chemotherapy plus venetoclax have been published: a phase 2 study evaluating venetoclax in combination with FLAG-IDA and a phase 2 study examining venetoclax combined with CPX-351. Composite complete remission occurred in 64% and 39% of patients, and the median overall survival was 12 months and 6 months, in each study, respectively. However, the activity of venetoclax in combination with HAM had not been prospectively investigated.

Added value of this study

To the best of our knowledge, the RELAX study is the first prospective clinical trial to combine HAM with venetoclax in patients with relapsed or refractory acute myeloid leukaemia. Interpreted alongside previously reported activity of venetoclax in combination with FLAG-IDA and CPX-351, HAM plus venetoclax achieved encouraging response rates while maintaining a manageable safety profile. The high proportion of patients who were able to undergo allogeneic haematopoietic cell transplantation (HCT) in ongoing remission is remarkable. Single-agent venetoclax maintenance appeared feasible and showed some activity in patients with favourable-risk disease.

Implications of all the available evidence

The RELAX trial, supported by previously published studies, provides further evidence that the combination of intensive chemotherapy with venetoclax can achieve remissions in a substantial proportion of patients with relapsed or refractory acute myeloid leukaemia. Combining intensive chemotherapy regimens with venetoclax seems to be a promising bridge to allogeneic transplantation, together inducing deep and durable remissions. Compared with immediate allogeneic HCT with sequential conditioning, remission induction using intensive chemotherapy regimens with venetoclax might offer advantages for patients with proliferative but *FLT3*-wildtype disease or those without a readily available stem cell donor.

antileukemic activity and has emerged as a key therapeutic agent in patients with newly diagnosed acute myeloid leukaemia ineligible for intensive chemotherapy.[5,6] In patients with relapsed or refractory acute myeloid leukaemia treated with venetoclax plus hypomethylating agents or venetoclax plus low-dose cytarabine, composite complete remission rates range around 33%, with a median overall survival of up to 6·6 months.[7] Venetoclax, which is being developed and approved for less intensive treatment, was also tested in combination with intensive chemotherapy. The CAVEAT trial evaluated venetoclax in combination with cytarabine plus idarubicin 5+2 induction chemotherapy in older patients (aged 63–80 years).[8] Kadia and colleagues assessed venetoclax in combination with cladribine, high-dose cytarabine, and idarubicin in patients with newly diagnosed acute myeloid leukaemia, as well as in combination with CPX-351 in patients with relapsed or refractory acute myeloid leukaemia,[9,10] and Mantzaris and colleagues combined venetoclax with 7+3 induction chemotherapy in younger patients with newly diagnosed acute myeloid leukaemia.[11] All these regimens were shown to be safe and active.[8–11] DiNardo and colleagues studied venetoclax in combination with FLAG-IDA, showing promising activity in both newly diagnosed and relapsed or refractory acute myeloid leukaemia.[12–14]

HAM is an established salvage regimen used in patients with relapsed or refractory acute myeloid leukaemia, not including fludarabine, such as in FLAG-IDA, or etoposide, such as in mitoxantrone, etoposide, and cytarabine. Both fludarabine and etoposide have not shown additional antileukemic activity in randomised trials.[15,16]

Based on the promising results seen with venetoclax in combination with less intensive and intensive chemotherapy, we aimed to evaluate the safety and activity of combining venetoclax with HAM in patients with relapsed or refractory acute myeloid leukaemia.

Methods

Study design and participants

This investigator-initiated, multicentre, open-label, single-arm, phase 1/2 trial was conducted at 12 hospitals in Germany (appendix p 2). Patients aged 18–75 years with relapsed acute myeloid leukaemia (ie, haematological relapse from first or second complete remission including patients with relapse after allogeneic haematopoietic cell transplantation [HCT]) or primary refractory disease (ie, no response after one or two courses of standard intensive induction chemotherapy, dose expansion only) were eligible. Patients had to be considered medically fit for intensive chemotherapy,

See Online for appendix

defined by an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, a life expectancy of more than 3 months, adequate hepatic function (ie, serum alanine aminotransferase and aspartate aminotransferase and bilirubin ≤2·5×upper limit of normal [ULN]), adequate renal function (ie, serum creatinine ≤1·5×ULN or creatinine clearance ≥50 mL/min, according to the Cockcroft Gault formula), and being afebrile and haemodynamically stable. Patients were required to understand and be willing to provide written informed consent. Male patients were eligible if they refrained from unprotected sex and sperm donation from the time of informed consent to 30 days after the last dose of study drug. Female patients were eligible only if they met at least one of the following criteria: a negative serum pregnancy test; postmenopausal status; history of bilateral ovariectomy, with or without hysterectomy; use of a contraception method with a Pearl index of <1%; or sexual abstinence. The scientific rationale for contraception requirements and exclusion for pregnancy and lactation was the teratogenic and embryotoxic potential of the study drugs. Patients with CNS involvement, isolated extramedullary disease, active graft-versus-host disease, and a cumulative previous exposure to anthracyclines of more than 410 mg/m² doxorubicin equivalents were excluded (appendix pp 3–5).

Patients sex was self-reported; options were male or female. Data on gender and race and ethnicity were not collected. There was no patient or public involvement in the study design, conduct, and reporting. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review committee of the TUD Dresden University of Technology (EK331072019). This trial is registered with EUDRA-CT, 2018–003025–28, and ClinicalTrials.gov, NCT04330820, and is completed.

Procedures

Phase 1 applied a 3+3 dose-escalation design to determine the maximum tolerated dose and recommended phase 2 dose. Four dose-escalation cohorts were examined: dose level –1, cytarabine 100 mg/m² continuous intravenous infusion on days 4–10; dose level 1, cytarabine 200 mg/m² continuous intravenous infusion on days 4–10; dose level 2, cytarabine 500 mg/m² intravenously twice a day on days 3–5; and dose level 3, cytarabine 1000 mg/m² intravenously twice a day on days 3–5. All patients received venetoclax 400 mg orally once a day on days 1–14, ramped-up over 3 days (patients treated within dose level –1 would have received venetoclax on days 1–10 only), and mitoxantrone 10 mg/m² intravenously once a day on days 5–7 (appendix p 6). The evaluation period for dose-limiting toxicities was defined as days 1–45. Dose-limiting toxicities were defined as CTCAE grade ≥3 non-haematological toxicities possibly related to venetoclax, clinical tumour lysis syndrome, and/or CTCAE grade 4 haematological toxicities (absolute neutrophil count <0·5×10⁹ cells/L or platelets <25×10⁹ cells/L) not recovered by day 45 in the absence of active disease (morphologic leukaemia-free state). Patients with composite complete remission not undergoing allogeneic HCT for post-remission treatment were eligible for venetoclax maintenance therapy (venetoclax 400 mg orally once a day on days 1–28, up to 12 28-day courses). Patients enrolled in the dose-expansion cohort were treated with the recommended phase 2 dose.

In patients with concomitant use of strong CYP3A inhibitors, the venetoclax dose was adjusted according to the summary of product characteristics. Venetoclax dose reductions or interruptions during single-agent venetoclax maintenance are provided in the study protocol (appendix pp 10–110). For patients with morphologic leukaemia-free state during early response assessment on days 18–21, the use of granulocyte-colony stimulating factor was permitted.

Harms were systematically defined, assessed as adverse events graded according to Common Terminology Criteria for Adverse Events version 5.0. Frequency and type of adverse events were monitored and prospectively collected in an electronic case report. Tumour lysis syndrome was defined and graded as per Cairo-Bishop classification.[17] Frequency and type of laboratory monitoring are specified in the study protocol (appendix p 10).

For response assessment and remission evaluation, bone marrow biopsies were performed on days 18–21 and 28–45, respectively. For response evaluation, European LeukaemiaNet (ELN) 2022 criteria were used.[18] Multiparametric flow cytometry-based measurable residual disease (MRD) was assessed centrally in the Study Alliance Leukemia reference laboratory. In line with the ELN consensus recommendations, we used a leukaemia-associated immunophenotype-based different from normal approach with a leukaemia-associated immunophenotype-specific limit of detection.[19,20] For some patients, molecular MRD was assessed locally as per standard of care using real-time quantitative PCR (RT-qPCR; *NPM1* and *CBFB*::*MYH11*) or next-generation sequencing (*BCOR*, *CEBPA*, *DDX41*, *GATA2*, *IDH2*, *RUNX1*, *SRSF2*, *STAG2*, and *U2AF1*). MRD negativity tested with next-generation sequencing was defined as less than 0·1% variant allele frequency.[20]

Reasons for patients to (prematurely) discontinue included interrupting venetoclax maintenance therapy for more than 28 days, withdrawing consent, or developing any intercurrent illness. Details of the study procedures are provided in the protocol (appendix p 10).

Outcomes

The primary endpoint of phase 1 was to determine the maximum tolerated dose and recommended phase 2 dose. The primary endpoint of phase 2 was the composite complete remission rate, which included complete remission and complete remission with incomplete

haematological recovery. Secondary objectives included overall survival (ie, time from first application of study drug to death; observation is censored at the end of the observational period in case of survival), proportion of patients undergoing allogeneic HCT following response (ie, number of patients with composite complete remission who underwent allogeneic HCT), relapse-free survival (time from composite complete remission to relapse or death among patients who had a response; observation is censored at the end of the observational period in case of relapse-free survival), duration of remission (time from composite complete remission to relapse), depth of remission (MRD-negative complete remission rate, number of patients who had MRD-negative composite complete remission), early mortality (number of patients who died within 30 days of first study drug administration), and tolerability (incidence and grade of adverse events). The cumulative incidence of relapse was also prespecified. However, we chose to report relapse-free survival only, which integrates relapse and death as events and therefore provides a more clinically meaningful estimate of disease control. Exploratory endpoints included the correlation of disease response with clinical features and genetic alterations.

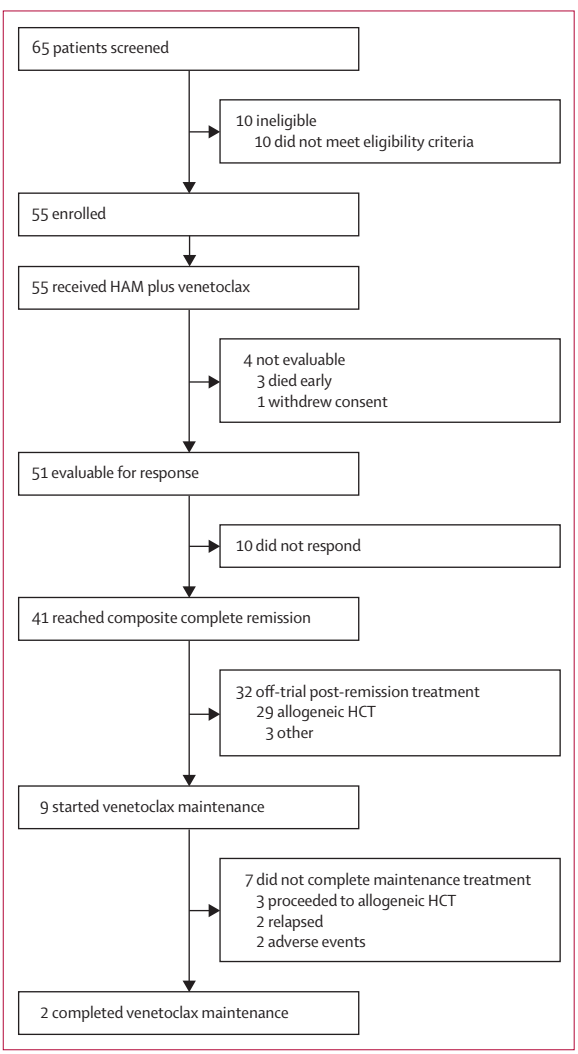


Figure 1: **Trial profile**
HAM=high-dose cytarabine and mitoxantrone. HCT=haematopoietic cell transplantation.

Statistical analysis

The sample size for phase 1 was calculated using the number of dose levels and the true probability of dose-limiting toxicities in the dose levels, with a minimum of four patients and a maximum of 18 patients being treated. The sample size for phase 2 was established using the A'Hern's single-stage design, testing a null hypothesis of complete remission and complete remission with incomplete haematological recovery ≤45% versus an alternative hypothesis of ≥65%; with a one-sided α of 0·05 and 80% power, 42 patients needed to be enrolled. Primary and secondary endpoints were assessed by intention to treat. All patients with exposure to venetoclax were part of the safety evaluation set. In all patients not evaluable for the primary endpoint (remission assessment not performed, eg, due to early death or withdrawal of consent, or remission assessment performed but not valid) the outcome was treated as not reaching composite complete remission. Time-to-event analyses (overall survival and relapse-free survival) were assessed using the Kaplan–Meier method. Median survival time (95% CI) and proportion of surviving patients (95% CI) were calculated and a log-rank test was used for comparison. Univariate analysis of composite complete remission rate and cofactors were evaluated using the Chi square test and presented with odds ratios (ORs) with 95% CIs. Analysis of the association between the timing of an event and predictor variables was done using cox regression models. Subgroup analyses (clinical and molecular subgroups) regarding the composite complete remission rate were not prespecified and were evaluated post-hoc. Post-hoc analyses were also conducted to: compare the overall survival of patients with de-novo acute myeloid leukaemia versus secondary or therapy-related acute myeloid leukaemia; overall survival of patients with or without previous allogeneic HCT; overall survival of patients with complete remission versus complete remission with incomplete haematological recovery; and overall survival in patients with ELN 2022 favourable-risk, intermediate-risk, and adverse-risk disease; and to evaluate patients undergoing allogeneic HCT in ongoing complete remission. Statistical analyses were performed using R version 4.3.3 and GraphPad Prism version 10.5.0.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

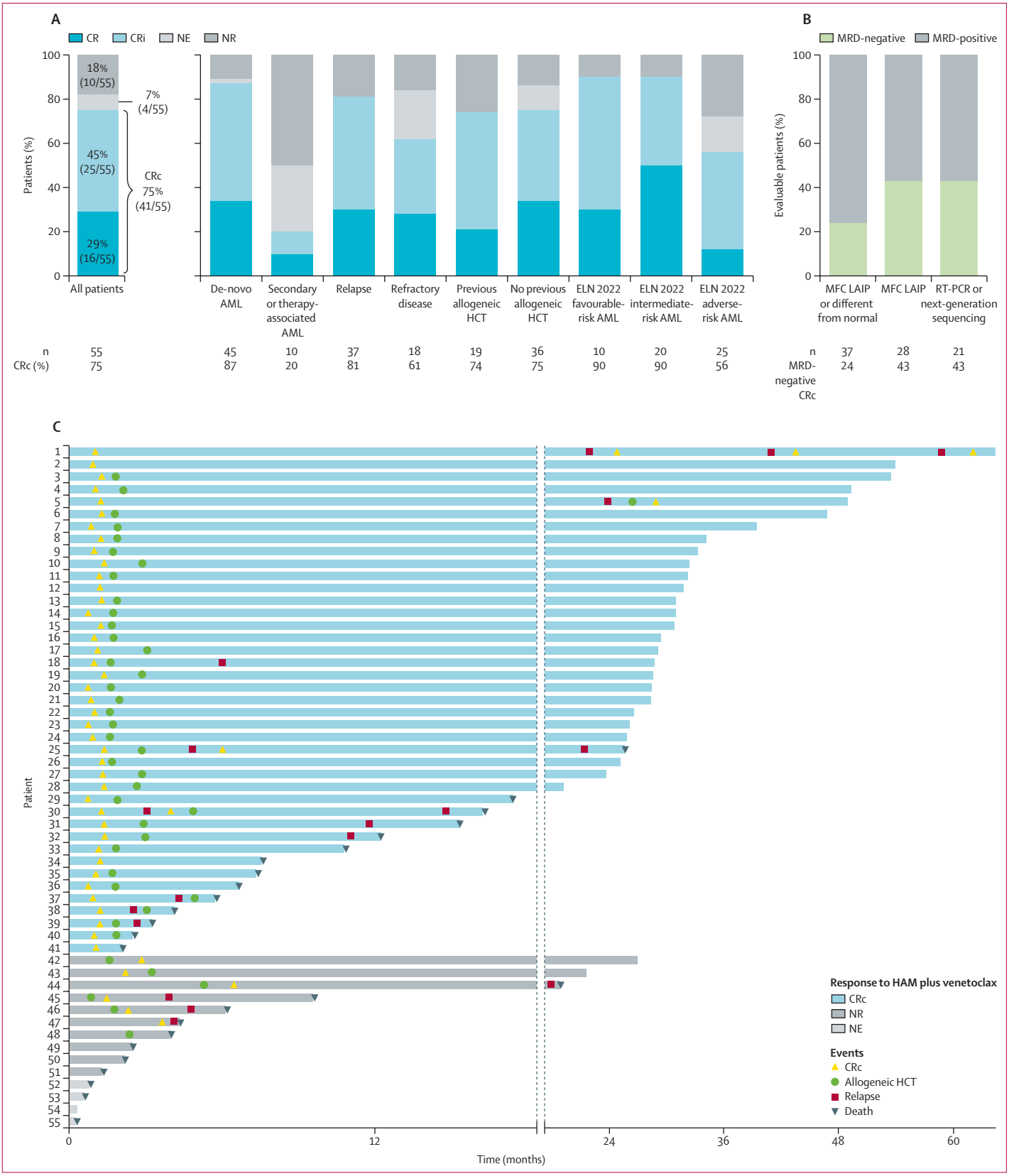
From April 6, 2020, to Aug 31, 2023, 65 patients were screened and 55 patients were enrolled (12 in phase 1 and 43 in phase 2; figure 1). As per Oct 15, 2025, the median follow-up was 30·8 months (IQR 26·6–34·1). Median age was 57 years (IQR 49·0–66·5). 30 (55%) of 55 patients were male and 25 (45%) were female. Most patients had de-novo acute myeloid leukaemia, whereas six (11%) of 55 were diagnosed with therapy-related acute myeloid leukaemia and four (7%) had a known antecedent myelodysplastic neoplasm or chronic myelomonocytic leukaemia. 17 (31%) of 55 patients could be classified as having acute myeloid leukaemia, myelodysplasia-related, based on WHO 2022 criteria.[21] According to the ELN 2022 risk stratification, ten (18%), 20 (36%), and 25 (45%) of 55 patients had favourable-risk, intermediate-risk, or adverse-risk acute myeloid leukaemia at diagnosis, respectively. 38 (69%) patients had acute myeloid leukaemia relapse (including 17 [45%] with a duration of first complete remission <12 months), whereas 17 (31%) were enrolled with primary refractory disease. The median number of previous therapy lines was 1 (range 1–3). All but one patient had received anthracycline and cytarabine-based intensive induction chemotherapy followed by high-dose cytarabine or allogeneic HCT for post-remission therapy. Two (4%) of 55 patients had previously been exposed to venetoclax, in combination with rituximab for chronic lymphocytic leukaemia, or in combination with FLAG-IDA for primary refractory acute myeloid leukaemia. Previous allogeneic HCT had been performed in 19 (35%) 55 patients (table 1).

12 patients were enrolled in the dose-escalation part of the trial. There were no dose-limiting toxicities in dose

	Patients (n=55)
Sex	
Female	25 (45%)
Male	30 (55%)
Age	
Median, years	57 (49·0–66·5)
≥60 years	21 (38%)
ECOG performance status	
<2	50 (91%)
2	5 (9%)
AML ontogeny	
De-novo AML	45 (82%)
AML with known antecedent MDS or chronic myelomonocytic leukaemia	4 (7%)
AML post-cytotoxic therapy	6 (11%)
AML, myelodysplasia related	17 (31%)
White blood cell count, ×10⁹ cells/L	2·81 (1·53–5·10)
Haemoglobin, mmol/L	5·71 (5·16–6·84)
Platelet count, ×10⁹ cells/L	64 (26–156)
Bone marrow blasts	35·5% (22–66)
Peripheral blood blasts	1% (0–18)
Extramedullary disease	4 (7%)
ELN 2022 risk classification at initial diagnosis	
Favourable	10 (18%)
Intermediate	20 (36%)
Adverse	25 (45%)
Genetic alterations at trial screening	
DNMT3A	19 (35%)
NPM1	11 (20%)
IDH2	11 (20%)
RUNX1	10 (18%)
FLT3	7 (13%)
GATA2	7 (13%)
ASXL1	6 (11%)
TP53	6 (11%)
IDH1	5 (9%)
NRAS	5 (9%)
SRSF2	5 (9%)
inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*	2 (4%)
Normal karyotype	17 (31%)
Cytogenetic abnormalities (intermediate risk)	17 (31%)
Complex karyotype	10 (18%)
MECOM rearrangement	3 (5%)
KMT2A rearrangement	1 (2%)
Karyotyping failed	5 (9%)
(Continued from previous column)	
Treatment failure	
Primary refractory disease	17 (31%)
Relapsed disease	38 (69%)
Relapsed disease (composite complete remission duration <12 months)	17/38 (45%)
Previous therapy	
Previous lines of therapy (range)	1 (1–3)
Induction therapy	
Intensive chemotherapy (anthracycline and cytarabine based)	54 (98%)
Less-intensive therapy	1 (2%)
Consolidation therapy*	
Intermediate-dose or high-dose cytarabine	16/29 (55%)
Allogeneic HCT	12/29 (41%)
Intermediate-dose or high-dose cytarabine and allogeneic HCT	1/29 (3%)
Previous midostaurin exposure	5 (9%)
Previous gemtuzumab ozogamicin exposure	7 (13%)
Previous venetoclax exposure	2 (4%)
Previous allogeneic HCT	19 (35%)

Data are n/N (%) and median (IQR) unless otherwise specified. Percentages might not total 100 due to rounding. AML=acute myeloid leukaemia. ECOG=Eastern Cooperative Oncology Group. ELN=European LeukemiaNet. HCT=haematopoietic cell transplantation. MDS=myelodysplastic neoplasm. *Only patients reaching complete remission after intensive induction therapy, without early relapse.

Table 1: **Patient demographics and baseline disease characteristics**


A
CR
CRi
NE
NR
Patients (%)
18% (10/55)
7% (4/55)
45% (25/55)
CRc 75% (41/55)
29% (16/55)
All patients
De-novo AML
Secondary or therapy-associated AML
Relapse
Refractory disease
Previous allogeneic HCT
No previous allogeneic HCT
ELN 2022 favourable-risk AML
ELN 2022 intermediate-risk AML
ELN 2022 adverse-risk AML
n 55 45 10 37 18 19 36 10 20 25
CRc (%) 75 87 20 81 61 74 75 90 90 56
B
MRD-negative
MRD-positive
Evaluable patients (%)
MFC LAIP or different from normal
MFC LAIP
RT-PCR or next-generation sequencing
n 37 28 21
MRD-negative CRc 24 43 43
C
Patient
Time (months)
Response to HAM plus venetoclax
CRc
NR
NE
Events
CRc
Allogeneic HCT
Relapse
Death

levels 1 or 2. In dose level 3, one of three patients had a haematological adverse event classified as a dose-limiting toxicity (ie, platelet count decreased to grade 4 by day 45). Additionally, three patients were treated in dose level 3, and no further dose-limiting toxicities occurred. Accordingly, the maximum tolerated dose was not reached, and dose level 3 was considered safe and defined as the recommended phase 2 dose (appendix p 6).

The composite complete remission rate was 75% (95% CI 61–85, 41 of 55 patients), with 16 of 55 patients (29%, 95% CI 18–43) reaching complete remission and 25 of 55 (45%, 32–59) reaching complete remission with incomplete haematological recovery. In post-hoc analyses, patients with de-novo acute myeloid leukaemia had a composite complete remission rate of 87% (95% CI 73–95) and patients with therapy-associated or secondary acute myeloid leukaemia of 20% (2–56). The composite complete remission rate in patients with relapsed acute myeloid leukaemia was 81% (65–92) and 61% (36–83) in patients with refractory disease. Responses were similar for patients with or without previous allogeneic HCT. The composite complete remission rate was 90% (56–100), 90% (68–98), and 56% (35–76) in patients with ELN 2022 favourable-risk, intermediate-risk, and adverse-risk acute myeloid leukaemia, respectively (figure 2A, table 2).

Of 41 patients reaching composite complete remission, 37 had available data on multiparametric flow cytometry-assessed MRD. Overall, multiparametric flow cytometry-assessed MRD-negative remissions were reached in nine of 37 patients (24%, 95% CI 12–42). A leukaemia-associated immunophenotype was not detectable during remission evaluation in 12 of 28 patients (43%, 25–63) with a leukaemia-associated immunophenotype that was definable during screening. 21 patients were evaluable for RT-qPCR or next-generation sequencing-based molecular MRD. Nine of 21 patients (43%, 22–66) had MRD-negative remissions (figure 2B, table 2).

Of 41 patients reaching composite complete remission, nine (22%) started venetoclax maintenance and 32 (78%) had post-remission therapy off-trial. Of these 32 patients, 29 (91%) underwent allogeneic HCT, one (3%) received cytarabine-based consolidation for post-remission therapy, one (3%) planned to proceed to allogeneic HCT but died, and one (3%) refused any further therapy after reaching remission. Of nine patients who started venetoclax maintenance, two (22%) relapsed while receiving venetoclax maintenance, five (56%) discontinued venetoclax maintenance in complete remission (three proceeded to subsequent allogeneic HCT and two had haematological adverse events), and two (22%) completed venetoclax maintenance. One patient with acute myeloid leukaemia with *CBFB*::*MYH11* fusion, had three episodes of molecular relapse after completing maintenance. In each episode the patient was successfully salvaged with venetoclax monotherapy. As per data cutoff, the patient was in MRD-negative complete remission without being allografted. Another patient, with acute myeloid leukaemia with mutated *NPM1* and several sub-clonal *TP53* alterations, was in ongoing MRD-negative complete remission without undergoing allogeneic HCT, after completing maintenance (figure 2C, table 2).

Of 41 patients reaching composite complete remission, 36 (88%) underwent subsequent allogeneic HCT, including those receiving short-term venetoclax bridging therapy; 32 (78%) underwent consolidative allogeneic

	Patients (n=55)
Response (remission evaluation at days 28–45)	
Composite complete remission	41/55 (75%, 61–85)
Complete remission	16/55 (29%, 18–43)
Complete remission with incomplete haematological recovery	25/55 (45%, 32–59)
No response	10/55 (18%, 9–31)
Non-evaluable for response	4/55 (7%, 2–18)
Early mortality (30 days)	3/55 (6%)
MRD response	
Composite complete remission and MRD negative (MFC LAIP-based DfN approach)	9/37 (24%, 12–42)
Composite complete remission and MRD negative (MFC LAIP only approach)	12/28 (43%, 25–63)
Composite complete remission and MRD negative (RT-qPCR or NGS)	9/21 (43%, 22–66)
Relapse-free survival	
Median, months	NR (21·0 to NR)
12 months	66% (49 to 78)
24 months	58% (42 to 72)
Duration of remission, months	4·6 (2·6 to 10·7)
Overall survival	
Median, months	NR (15·0 to NR)
12 months	65% (51 to 76)
24 months	56% (41 to 68)
Allogeneic HCT in follow-up	
Allogeneic HCT irrespective of response	42/55 (76%)
Allogeneic HCT after reaching complete response*	36/41 (88%)
Consolidative allogeneic HCT in ongoing remission*	32/41 (78%)
Time to consolidative allogeneic HCT in remission, days	59 (35–98, 49–82)

Data are n/N (%, 95% CI), n/N (%), rate (95% CI), median (IQR), or median (range, IQR). Percentages might not total 100 due to rounding. DfN=different from normal. HCT=haematopoietic cell transplantation. LAIP=leukaemia-associated immunophenotype. MFC=multiparametric flow-cytometry. MRD=measurable residual disease. NGS=next-generation sequencing. NR=not reached. RT-qPCR=real-time quantitative PCR. *Including patients receiving transient venetoclax maintenance.

Table 2: **Patient outcomes**

Figure 2: **Response rates and post-remission treatment and follow-up**
(A) Overall remission rates and post-hoc analyses by patient subgroups or baseline characteristics. (B) MRD responses. (C) Swimmer plot showing further treatment and follow-up. Percentages might not total 100 due to rounding. AML=acute myeloid leukaemia. CR=complete remission. CRc=composite complete remission. CRi=complete remission with incomplete haematological recovery. HAM=high-dose cytarabine and mitoxantrone. HCT=haematopoietic cell transplantation. MFC LAIP=multiparametric flow cytometry-assessed leukaemia-associated immunophenotype. MRD=measurable residual disease. NE=not evaluable. NR=no response. RT-qPCR=real-time quantitative PCR.

HCT in ongoing remission and four (10%) were allografted for subsequent relapse. The median time from initiation of treatment to consolidative allogeneic HCT in remission was 59 days (range 35–98, IQR 49–82).

As per data cutoff, ten (24%) of 41 patients had a relapse, including one with molecular relapse. Median duration of remission was 4·6 months (IQR 2·6–10·7). Four patients were salvaged successfully. 14 patients died after reaching composite complete remission: seven died due to relapse and seven died in remission due to complications associated with allogeneic HCT and/or infectious complications. Ten patients showed no response to HAM plus venetoclax. Four patients were not evaluable for response: three patients died in aplasia and one withdrew consent.

Median overall survival for the entire cohort was not reached (95% CI 15·0 to not reached), corresponding to a 12-month and 24-month overall survival rate of 65% (51 to 76) and 56% (41 to 68), respectively. Median relapse-free survival was not reached (21·0 to not reached). 12-month and 24-month relapse-free survival rates were 66% (49 to 78) and 58% (42 to 72), respectively (figure 3, table 2).

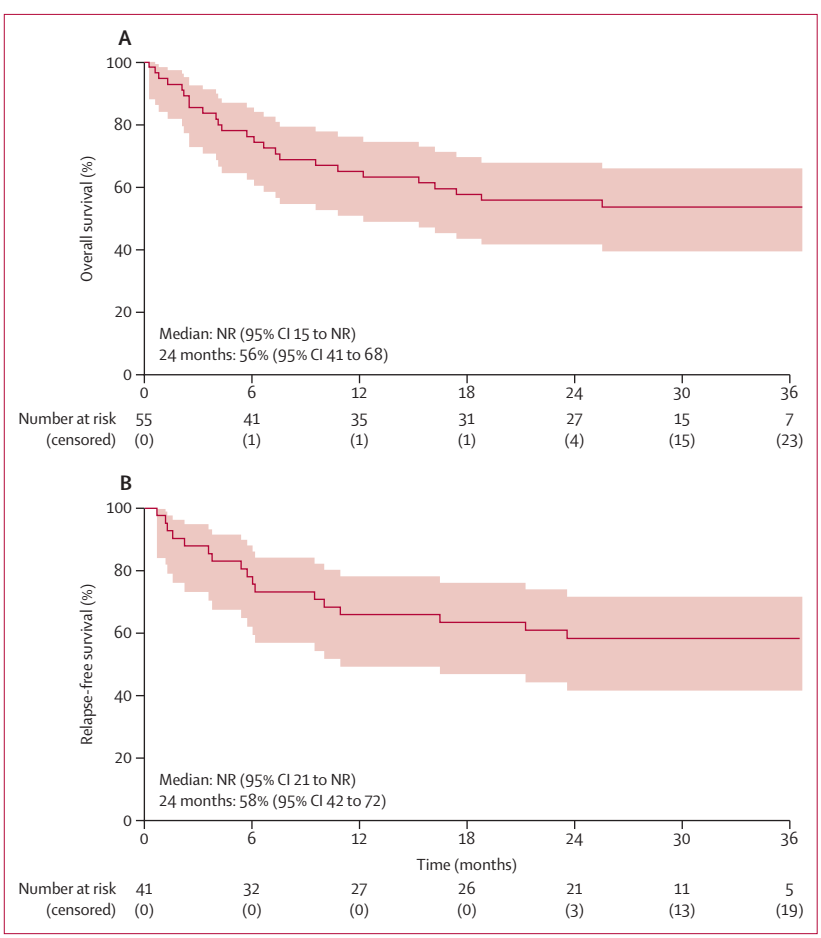


Figure 3: **Patient outcomes**
Overall survival (A) and relapse-free survival (B). NR=not reached.

Nearly all patients (96%) had at least one adverse event. Most patients (80%) had at least one non-haematological adverse event. The most common all-grade adverse events were febrile neutropenia (29 [53%] of 55 patients), pneumonia (12 [22%]), sepsis (12 [22%]), mucositis oral (12 [22%]), liver functions test abnormalities (eight [15%]), and nausea (eight [15%]; table 3). 15 serious adverse events were observed in 14 patients, with sepsis (n=6) and pneumonia (n=2) being the most common serious adverse events. No patients had tumour lysis syndrome, neither laboratory nor clinical. Potentially treatment-related deaths were reported in four (7%) of 55 patients, including sepsis (n=3) and pneumonia (n=1). Three patients died early; the corresponding 30-day mortality was 6% (three of 55 patients).

Among patients reaching composite complete remission, median time to neutrophil count recovery (absolute neutrophil count ≥0·5 cells×10⁹/L) was 33 days (range 23 days to not reached [by day 45]), and median time to platelet count recovery (platelet count ≥50 cells×10⁹/L) was also 33 days (range, 21 to not reached [by day 45]). Five (12%) of 41 patients had received granulocyte-colony stimulating factor.

Patient and disease characteristics grouped per response are summarised in the appendix (p 7). In post-hoc analyses, high composite complete remission rates were observed in patients with mutations in *NPM1*, *IDH1*, or *IDH2*, whereas composite complete remission rates in patients with *ASXL1*-mutated or *TP53*-mutated acute myeloid leukaemia or acute myeloid leukaemia with complex karyotype were lower (appendix p 7). As per univariable post-hoc analysis, patients with de-novo acute myeloid leukaemia were significantly more likely to reach composite complete remission with HAM plus venetoclax than patients with secondary or therapy-related acute myeloid leukaemia. By comparison, remission was significantly less likely to occur in patients with AML with complex karyotype or *TP53* mutations. Response to HAM plus venetoclax did not show an association with sex, age, previous allogeneic HCT, or presence of mutations in *ASXL1, DNMT3A*, *FLT3*, *IDH1*, *IDH2*, *NPM1*, or *RUNX1* (appendix p 7).

In a post-hoc analysis, median overall survival was not reached in patients with ELN 2022 favourable-risk and intermediate-risk disease, and 9·6 months in the adverse-risk group. The corresponding 24-month overall survival rates for patients with acute myeloid leukaemia with ELN 2022 favourable, intermediate, and adverse risk were 70%, 71%, and 46%, respectively. In patients who underwent allogeneic HCT in ongoing complete remission, median overall survival was not reached, corresponding to a 24-month overall survival rate of 75% (95% CI 56 to 87), as evaluated post-hoc. Overall survival in patients with de-novo acute myeloid leukaemia was similar to that in patients with therapy-associated or secondary acute myeloid leukaemia. In a post-hoc analysis, survival was similar for patients with or without

previous allogeneic HCT and patients reaching complete remission had a longer median overall survival than those reaching complete remission with incomplete haematological recovery (appendix p 8, table 2).

Evaluated post-hoc by univariable Cox regression, *TP53* alterations and complex karyotype showed an association with worse survival, whereas age, sex, acute myeloid leukaemia ontogeny, previous allogeneic HCT, and presence of mutations in *ASXL1, DNMT3A*, *FLT3*, *IDH1, IDH2, NPM1,* or *RUNX1* did not significantly affect survival (appendix p 9). In post-hoc analyses, median overall survival was numerically longer in patients with *NPM1*-mutated, *IDH1*-mutated, and/or *IDH2*-mutated acute myeloid leukaemia than in those with wildtype disease. Patients with acute myeloid leukaemia with *TP53* alterations or complex karyotype, or both, had significantly worse median overall survival (appendix p 9).

Discussion

The RELAX trial evaluated HAM in combination with venetoclax as a salvage treatment for medically fit patients with relapsed or refractory acute myeloid leukaemia. HAM plus venetoclax appeared to be safe in this setting and showed promising activity in medically fit patients with relapsed or refractory acute myeloid leukaemia, inducing high remission rates, thus enabling transition to allogeneic HCT. Safety and activity appear encouraging when considered alongside published results from other intensive salvage regimens, thereby providing a novel treatment approach that might help to improve long-term outcomes in these patients with high medical need.

Compared with historical salvage treatment with HAM alone, with composite complete remission rates around 50% and a mean weighted overall survival of 5·4 months, HAM plus venetoclax improved outcomes, with a composite complete remission rate of 75% and a median overall survival that was not reached, corresponding to a 24-month overall survival rate of 56%.[1,2,5,6]

Studies have provided alternative approaches to combine intensive chemotherapy with venetoclax in patients with relapsed or refractory acute myeloid leukaemia. DiNardo and colleagues evaluated venetoclax in combination with FLAG-IDA in patients with acute myeloid leukaemia, including 61 patients with relapsed or refractory acute myeloid leukaemia, many of whom had adverse-risk genetics.[14] The composite complete remission rate was 64%, median overall survival was 12 months, and 57% of patients proceeded to allogeneic HCT. Based on the German venetoclax registry, Shahswar and colleagues retrospectively compared FLA-IDA with FLA-IDA in combination with venetoclax as a salvage treatment for 37 patients with relapsed or refractory acute myeloid leukaemia.[22] Patients treated with FLA-IDA plus venetoclax had a composite complete remission rate of 59% and a median overall survival of 12 months. Similarly, Wille and colleagues retrospectively assessed 18 patients with relapsed or refractory acute myeloid leukaemia treated with FLAG-IDA plus venetoclax. The

	Grade 1–2	Grade 3	Grade 4	Grade 5
Febrile neutropenia	0	29 (53%)	0	0
Pneumonia	0	10 (18%)	1 (2%)	1 (2%)
Sepsis	0	7 (13%)	2 (4%)	3 (6%)
Mucositis oral	5 (9%)	7 (13%)	0	0
Nausea	6 (11%)	2 (4%)	0	0
LFT abnormalities*	1 (2%)	5 (9%)	2 (4%)	0
Oedema in limbs	5 (9%)	2 (4%)	0	0
Rash maculo-papular	5 (9%)	1 (2%)	0	0
Fatigue	6 (11%)	0	0	0
Hypokalaemia	3 (6%)	3 (6%)	0	0
Diarrhoea	2 (4%)	3 (6%)	0	0
Back pain	3 (6%)	1 (2%)	0	0
Insomnia	3 (6%)	1 (2%)	0	0
Syncope	0	5 (9%)	0	0
Neutropenic enterocolitis	0	3 (6%)	0	0
Abdominal pain	2 (4%)	1 (2%)	0	0
Hypophosphataemia	1 (2%)	2 (4%)	0	0
Pleural effusion	0	2 (4%)	0	0
Acute myocardial infarction	0	1 (2%)	0	0
Anal abscess	0	1 (2%)	0	0
Anal haemorrhage	0	1 (2%)	0	0
Apocrine breast carcinoma	0	1 (2%)	0	0
Atrial fibrillation	0	1 (2%)	0	0
COVID-19	1 (2%)	1 (2%)	0	0
Chronic kidney disease	0	1 (2%)	0	0
Decreased appetite	0	1 (2%)	0	0
Dizziness	1 (2%)	1 (2%)	0	0
Epistaxis	1 (2%)	1 (2%)	0	0
Gingival pain	0	1 (2%)	0	0
Hallucinations	0	1 (2%)	0	0
Hepatic candidiasis	0	1 (2%)	0	0
Hypertension	1 (2%)	1 (2%)	0	0
Hypoalbuminemia	0	1 (2%)	0	0
Musculoskeletal pain	0	1 (2%)	0	0
Osteonecrosis	0	1 (2%)	0	0
Pericardial effusion	0	0	1 (2%)	0
Proctalgia	0	1 (2%)	0	0
Pulmonary oedema	0	0	1 (2%)	0
Pyrexia	3 (6%)	1 (2%)	0	0
Right ventricular dysfunction	0	1 (2%)	0	0
Sinus tachycardia	0	1 (2%)	0	0
Spinal cord compression	0	0	1 (2%)	0
Vertigo	1 (2%)	1 (2%)	0	0
Weight gain	1 (2%)	1 (2%)	0	0

Grade 1–2 adverse events reported in more than 10% of patients. All grade 3–5 adverse events are reported. LFT=liver function test. *LFT abnormalities include aspartate aminotransferase increased, alanine aminotransferase increased, γ-glutamyl transferase increased, alkaline phosphatase increased, and blood bilirubin increased.

Table 3: **Non-haematological treatment-emergent adverse events**

composite complete remission rate was 72%, median overall survival (with a short follow-up of <6 months) was not reached, and the 6-month overall survival rate was 80%.[23] Using another chemotherapy backbone, Kadia and colleagues investigated venetoclax in combination with CPX-351 in 33 patients with relapsed or refractory acute myeloid leukaemia, including a high proportion of patients with adverse risk cytogenetics and previous venetoclax exposure. Patients treated with CPX-351 plus venetoclax had a composite complete remission rate of 39% and a median overall survival of 6 months, and 11 patients had subsequent allogeneic HCT.[10] Encouragingly, with HAM plus venetoclax, we observed a composite complete remission rate of 75%, a median overall survival of not reached, a 24-month overall survival rate of 56%, and a high rate of transition to allogeneic HCT. However, differences in patient age, adverse-risk genetics, previous lines of treatment, and previous exposure to venetoclax limit direct cross-trial comparisons.

With a leukaemia associated immunophenotype-based different from normal approach, 24% of patients treated with HAM plus venetoclax reached an MRD-negative complete remission, whereas rates of multiparametric flow cytometry-assessed MRD-negative remission observed with FLAG-IDA plus venetoclax and CPX-351 plus venetoclax were 74% and 46%, respectively.[10,14] Nevertheless, variations in methodology and baseline characteristics preclude definitive cross-trial comparisons.

Preclinical data indicate synergistic effects against resistant leukemic stem cells when combining venetoclax and mitoxantrone, providing a possible rationale for the activity seen with HAM plus venetoclax.[24] Likewise, there are data showing strong synergy, probably through mitochondrial priming and DNA damage, when venetoclax and idarubicin are combined.[25]

Responses observed with HAM plus venetoclax were encouraging across most clinical and molecular subgroups, including heavily pretreated patients and those with previous allogeneic HCT. Patients with ELN 2022 favourable-risk and intermediate-risk acute myeloid leukaemia had remissions rates of 90%. Responses observed in patients with adverse-risk acute myeloid leukaemia were lower but still encouraging, with 56%. Patients with evidence of mutations in *NPM1* or *IDH1* or *IDH2*, or combinations of these mutations, had a more favourable outcome with HAM plus venetoclax, whereas the presence of a complex karyotype or *TP53* alterations predicted inferior survival. Both findings are in line with previous reports evaluating venetoclax in combination with intensive chemotherapy.[8,12–14]

Most patients treated with HAM plus venetoclax could proceed to allogeneic HCT, 88% after reaching composite complete remission, and 78% in ongoing complete remission. Rates of transition to allogeneic HCT after HAM plus venetoclax are encouraging when interpretated alongside rates reported for intensive chemotherapy alone, and those observed with FLAG-IDA plus venetoclax in relapsed or refractory acute myeloid leukaemia.[1,12,14] In our study, median overall survival in patients undergoing allogeneic HCT in ongoing complete remission was not reached, corresponding to a 24-month overall survival of 75%. With remission induction and subsequent allogeneic HCT remaining the preferred approach for patients with relapsed or refractory acute myeloid leukaemia in many treatment centres,[26,27] we consider HAM in combination with venetoclax a novel, highly effective bridge-to-transplant regimen for medically fit patients.

Of nine patients receiving venetoclax maintenance, only two relapsed. Two patients who completed maintenance had ongoing remissions without being allografted, one of whom could be salvaged three times with venetoclax monotherapy after completing maintenance. These findings are in line with previous reports showing safety and activity with venetoclax maintenance in acute myeloid leukaemia, not only in combination with HMA, but also as a monotherapy.[28–30] Accordingly, HAM plus venetoclax with subsequent venetoclax monotherapy maintenance could be discussed as an option for patients without a readily available donor or with other factors arguing against (immediate) allogeneic HCT.

The HAM venetoclax regimen could be considered safe in this setting. Primarily, infectious complications were reported, with febrile neutropenia, pneumonia, and sepsis being the most common all-grade adverse events with four potential treatment-related deaths due to sepsis and pneumonia. The early mortality rate was low (6%), which is similar to the rate observed with FLAG-IDA plus venetoclax and superior to the rate from intensive chemotherapy regimens without venetoclax; however, the latter finding is likely to be confounded by recently improved supportive care measures.[1,12,14,31] The median time to neutrophil and platelet count recovery was 33 days, with only 12% of patients having received granulocyte-colony stimulating factor. These findings are similar to those observed with HAM alone, and those seen with FLAG-IDA plus venetoclax combinations.[2,12,14]

As this study was a phase 1/2 trial without a control group or comparator, conclusions from some of the post-hoc subgroup analyses, such as factors predicting outcome with HAM plus venetoclax, are limited. A pooled analysis of patients with relapsed or refractory acute myeloid leukaemia treated with HAM (or other intensive chemotherapy regimens) in combination with venetoclax within clinical trials or in real-world settings could therefore be valuable. The results also provide a basis for future studies evaluating venetoclax in combination with intensive salvage chemotherapy before allogeneic HCT, either as part of remission induction or as sequential conditioning, in patients with relapsed or refractory acute myeloid leukaemia.

Contributors

CR, JS, MW, MiK, and MB: literature search, study design, and funding acquisition. LR, CS, JHM, MS, LF, BS, MK, AB, AR, MHa, AHö, SK, KSE, MHä, AHa, FF, MaK, SZ, DK, JMM, KS, JS, UP, MvB, MAR, FS, CDB, HS, MW, MB, and CR: patient enrolment, patient treatment, and data collection. MvB, MAR, UO, LW, CT, SH, DP, and LR: laboratory investigation. LR, AH, FF, MiK, SZ, and CR: data analysis and data interpretation. LR and CR: accessing and verifying the underlying data, writing of the original draft, and visualisation. All authors: writing, review, and editing. All authors had full access to all the data in the study and had final responsibility to submit for publication.

Declaration of interests

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Data sharing

De-identified individual participant data and related study materials will be made available from the corresponding author on reasonable request and subject to institutional and regulatory approvals.

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